

Areas of uncertainties and unmet needs in bipolar disorders: clinical and research perspectives



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This Review discusses crucial areas related to the identification, clinical presentation, course, and therapeutic management of bipolar disorder, a major psychiatric illness. Bipolar disorder is often misdiagnosed, leading to inappropriate, inadequate, or delayed treatment. Even when bipolar disorder is successfully diagnosed, its clinical management presents several major challenges, including how best to optimise treatment for an individual patient, and how to balance the benefits and risks of polypharmacy. We discuss the major unmet needs in the diagnosis and management of bipolar disorder in this Review, including improvement of adequate recognition and intervention in at-risk and early-disease stages, identification of reliable warning signs and prevention of relapses in unstable and rapid cycling patients, treatment of refractory depression, and prevention of suicide. Taken together, there are several promising opportunities for improving treatment of bipolar disorder to deliver medical care that is more personalised.

Introduction

Bipolar disorder, previously known as manic-depressive illness, belongs to a group of severe, recurrent affective disorders that are among the leading causes of disability in working-age adults. Including the different variants of the disorder, bipolar disorder affects 2–3% of the world's population irrespective of nationality, ethnic or cultural origin, and socioeconomic status.¹ Despite its characteristic phenotype, bipolar disorder is often misdiagnosed, leading to inappropriate or delayed treatments—a situation that can have negative and often devastating health and social consequences.^{2,3} The substantial disease burden attributable to bipolar disorder is amplified by additional, often multiple, psychiatric and physical comorbidities and premature mortality caused by suicide and cardiovascular diseases.^{4,5}

Typically, bipolar disorder evolves from an asymptomatic at-risk stage to the emergence of prodromal symptoms, a term commonly used to describe the symptoms and signs that precede episode onset, in adolescence or early adulthood, followed by a first affective episode and eventually an unpredictable and relapsing course throughout the lifespan. The long-term course of bipolar disorder is highly variable, associated with both interindividual variation and heterogeneity between patients. Over a lifetime, a patient might have many forms of the illness including mixed emotional states, psychosis, depressive and manic or hypomanic episodes, and rapid cycling between such episodes. Patients vary greatly in the severity of their symptoms, the duration of episodes, the number of episodes, the degree of recovery between episodes, and the pattern of polarity.^{6,7} Furthermore, a large degree of comorbidity exists with these patients, including substance abuse and somatic illness.

Even when successfully diagnosed, the management of bipolar disorder provides major challenges including how best to optimise treatment for an individual patient, and how to balance the benefits and risks of drug therapy. Despite an increasing number of treatments, full recovery is infrequent and incomplete symptomatic remission with a high degree of individual variability is often the

clinical norm. A substantial proportion of patients do not respond adequately to drug monotherapy, and combinations of drugs are often required to achieve acute stability and reduce relapses. Given the wide range of phenotypic expressions and responses to treatment associated with bipolar disorder, complex medication regimens are commonplace.^{8,9} Although pharmacotherapy forms the foundation for successful treatment of the disorder, adjunctive psychosocial interventions can also be useful for acute depressive episodes. Although there are no first-line or maintenance psychosocial treatment options for acute bipolar depression, on average, adjunctive psychosocial treatments (eg, psychoeducation, cognitive behavioural therapy, family-focused therapy, and interpersonal and social-rhythm therapy) reduce recurrence by approximately 15%.¹⁰

There is increasing recognition that even during remitted periods, patients have frequent subsyndromal mood symptoms (eg, mood symptoms of minor severity, symptoms less severe than hypomania, or minor depression)¹¹ and an impaired quality of life. Furthermore, despite great advances in the understanding of mental disorders in general, the precise mechanisms underlying bipolar disorder and the response to treatment at the genetic, cellular, or neuroanatomical level remain elusive, with valid animal models non-existent.¹²

In this Review by members of the European College of Neuropsychopharmacology Bipolar Network,¹³ we address several important unmet clinical needs in prevention, diagnostic assessment, and therapeutic intervention in bipolar disorder. Specifically, we discuss crucial areas related to the early recognition and intervention in at-risk stages, the identification of reliable warning signs and prevention of relapses in unstable (rapid cycling) bipolar disorder, and management of depression, suicidality, and reduced life expectancy. This Review will not only identify these areas of uncertainty but also offer guidance for solving the problem. Our focus is both practical and on bipolar disorder as it is currently clinically conceptualised. We do not, therefore, cover advances in neuroscience to understand the basic mechanisms of mood instability,

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new ways of measuring the phenotype, or how together these advances might lead to a reclassification of the disorder, these are covered elsewhere.^{14,15}

Improved identification of at-risk populations

A major goal of modern medicine is primary and secondary prevention of disease. This aim has successfully been accomplished for many infections with vaccination programmes, and more recently, programmes targeting cardiovascular risk factors such as lifestyle, smoking, and high cholesterol. For psychiatric disorders in general, and for bipolar disorder in particular, identification of at-risk populations has been difficult. However, in the past decade, there has been an increasing focus on research into precursors of bipolar disorders and attempts to clarify early symptoms and illness trajectory.¹⁶ For example, the bipolar prodrome is mainly characterised by symptoms of the subsequent mood episode.¹⁶ However, there remains considerable uncertainty about how to identify high-risk groups and no effective preventive measures are available. The most promising approach so far has been to follow up children and adolescents who have parents with bipolar disorders,^{17,18} but the clinical benefits of identification of at-risk youth populations remains to be seen. The positive predictive value of early symptoms or patterns of clinical characteristics is low and it is therefore very difficult to differentiate between adolescents with unspecific mental symptomatology as part of healthy development, and those who later develop bipolar disorder. However, this area of research is active and there are promising findings using brain imaging biomarkers; specific patterns of brain activation in individuals of 10–12 years of age are associated with later development of mental symptoms,¹⁹ although, again, not specific for bipolar disorder. A delayed development of the functional connectome network has been identified. However, this finding was not specific for bipolar disorder. Case-control classification using cognitive performance, multimodal imaging features (eg, cortical thickness, surface area, and grey matter density maps), and polygenic risk scores increased classification performance, suggesting a complementary predictive value for bipolar disorder.²⁰

In common with other mental disorders, large unselected youth cohorts are needed for studies. Prospective, non-biased registration of symptomatology during childhood and adolescence, and comparing people who later develop bipolar disorder with people who remain healthy, will be informative. However, the large sample size, long duration, and multicohort coordination necessary to reach this goal make it practically difficult. Some large cohorts have been established, such as the Mother and Child study,²¹ a birth cohort of more than 100 000 individuals. Other similar cohorts are being established, and systematically investigating aspects related to later development of bipolar disorder will have great importance. Diagnosis in parents constitutes the

selection criteria of ongoing studies for at-risk populations. This risk is mainly because of heritable factors. Thus, with the constantly increasing number of genetic loci associated with the disorder from large international bipolar disorder genetic consortia, such as the Psychiatric Genomics Consortium,²² it might be possible to identify at-risk people by use of genotyping in the future.

Early intervention

Although the course of bipolar disorder is heterogeneous, there is some evidence for distinct stages of clinical progression, including an increased risk of developing dementia,²³ supporting the theory of bipolar disorder as a progressive neurological illness with detrimental effects on brain function. Consequently, early intervention aiming to stop or delay the course of illness is appealing. However, clinical effects of early interventions have rarely been investigated in bipolar disorder, representing a major knowledge gap. No double-blind, placebo, or active controlled trial has been published, to our knowledge, on the effects of pharmacological or psychological interventions on primary clinical outcomes in patients with first-episode mania. In a randomised controlled trial, early intervention following first hospitalisations for mania or bipolar disorder significantly decreased the risk of re-hospitalisation, improved adherence to medication, and increased satisfaction with care (as provided in a specialised mood disorder clinic combining pharmacological treatment and group psychoeducation) compared with standard care.²⁴ The effects were especially pronounced among young patients (aged 18–25 years), although the validity of this finding is limited on the basis of the small number of young participants ($n=29$, 18.4% of total sample).²⁵ Furthermore, a 2017 randomised trial in Australia including patients with first-episode mania found that maintenance treatment with lithium monotherapy was superior to quetiapine for clinical secondary outcome measures of depression, quality of life, functioning, and global impression.²⁶

In addition to the findings from these randomised controlled trials, a substantial body of observational data suggests that early intervention might improve disease course and outcome.²⁴ Starting a course of lithium early after a single manic or mixed episode is associated with an increased proportion of patients with a response to lithium compared with patients who had a later start.²⁷ In a patient with first-episode mania, it is suggested that combined clinical and psychosocial interventions have positive effects on symptomatic and functional recovery,^{28,29} including cognitive functioning.³⁰ Delay to first treatment is associated with poorer outcomes.³¹ The occurrence of multiple previous episodes seems to be a risk factor for non-response to various pharmacological treatments.^{32–34} Mood stabilisers prescribed for bipolar disorder might have neuroprotective abilities^{35,36} and patients could benefit from psychoeducation before potential cognitive disturbances occur during the long-term course of illness.³⁷ Patients with first-episode

bipolar disorder present with increased psychosocial function compared with patients with multiple episodes³⁸ who rarely achieve functional recovery.³⁹ Evidently, results from such observational studies are influenced by bias of various kinds and potential confounding factors.

In summary, there is a need for large, multicentre randomised trials in patients with first-episode bipolar disorder comparing the maintenance effects of lithium with other maintenance mood stabilisers and randomised controlled trials comparing psychological interventions. Future studies on early intervention in bipolar disorder should not only focus on improving the outcome of the disorder but also on decreasing the risk of comorbid general medical illnesses as natural causes of death, which are the most common cause of life-years lost from adolescence in bipolar disorder.⁴⁰

Delay of correct diagnosis in clinical practice

There is often a delay in the diagnosis of bipolar disorder of, on average, 8–10 years. This is crucially important as it can delay effective treatment and worsen prognosis. Diagnosis delay is a particular problem in patients with younger age of onset. A large collaborative study of 529 patients reported that the 50% of patients who had onset of illness before 18 years of age were more likely to have long delays to first treatment and therefore spend more time depressed, be more severely depressed, have more cycling between mania and depression, and have fewer days with a euthymic mood than those of an older age.³¹ A collaborative French study found a mean duration of untreated bipolar disorder of 9·6 years (SD 9·7; median 6), which was longer for patients presenting with hypomania rather than depressive or manic episodes (median 13 vs 8 years).⁴¹ The reasons for the delay are likely to include the difficulties in diagnosing less severe degrees of mood instability or hypomania, particularly in younger patients. However, the delay exists for patients even after contact with mental health-care services. One study found the median time from first treatment contact within psychiatric services to the first diagnosis with a manic episode or bipolar disorder to be 0·92 years (IQR 0·12–2·65).⁴²

There are perhaps always going to be difficulties reaching a diagnosis when it is often based on retrospective subjective recall, in the absence of manifest manic symptoms and objective diagnostic biomarkers. However, it is possible that clinical improvements can be achieved by better recognition of early symptoms⁴³ and higher quality clinical practice.

Management of bipolar disorder

Adherence to therapy in young people and strategies for improvement

Even the most effective treatments can only be beneficial if they are acceptable to the patient and the patient adheres to the recommended therapy. Adherence to therapy is a major issue in long-term health conditions and can be a

problem for younger people who have been diagnosed with cancer, diabetes, asthma, or bipolar disorder. In people with bipolar disorder, this problem can be compounded by negative views of, and stigma around, therapies that include lithium. The careful management of the introduction of long-term drug therapies and dealing with patients' beliefs and concerns is likely to be crucially important for long-term adherence, and there is evidence that this is especially relevant in bipolar disorders.^{44,45} There is some evidence that a range of brief interventions can increase treatment adherence, including some specific psychosocial interventions such as family-focused therapy, which might conceivably be one mechanism with beneficial effects in reducing manic symptoms.^{46,47} The effectiveness of interventions aimed at increasing adherence might be enhanced by including tools that personalise the probable benefits and risks of treatment by integrating trial and observational evidence with individual patient-derived utilities. Similar approaches might be helpful in increasing adherence for therapies that have a negative public profile and, therefore, increase patient concerns. Negative public profiles are a common problem for drugs, such as lithium, used to treat mental illness.^{48,49} Improving adherence is one area in which working closely (and imaginatively) with patient groups is likely to be of great importance.⁵⁰

Treatment of bipolar depression

The treatment of bipolar depression remains a challenge. Patients spend more time depressed than manic or hypomanic, and the residual symptoms of depression are extremely common. However, there are fewer treatments for the depressive phase than for the manic phase, and time to remission takes much longer. The depressive phase of bipolar disorder also accounts for the majority of suicide attempts (see section on suicide prevention), and unsuccessful treatment of bipolar depression can cause unnecessary suffering and morbidity. Clinical features to take into account when treating a given patient with bipolar depression include bipolar subtype (I or II), atypical symptoms, melancholic symptoms, catatonia, psychosis, post-partum onset, mixed symptoms, anxiety, suicidality, rapid cycling, seasonality, and predominant polarity. In patients with previous episodes, it is important to get a full history of response to previous treatments. The most recently published treatment guidelines support the use of quetiapine in bipolar type I and type II depression, lurasidone in bipolar type I depression, and lamotrigine in bipolar type II depression, in combination with lithium in bipolar type I depression.^{51,52} Olanzapine alone or in combination with fluoxetine is generally advised as second-line treatment. Lithium and valproate can have limitations as monotherapies, but are effective in combination. The controversy surrounding the role of antidepressants remains,⁵³ but data support the use of the modern compounds as adjunctive treatments in patients with bipolar depression without rapid cycling or mixed features.⁵⁴ Electroconvulsive therapy proved superior to an

algorithm-based pharmacological treatment in patients with difficult-to-treat conditions.⁵⁵ Brain stimulation techniques are under investigation,⁵⁶ but at the present time the most promising approach seems to be from within the ketamine framework (glutamate antagonists).⁵⁷ Although it is too early to recommend routine use of ketamine and derivatives, there are a number of compounds in the pipeline that could become available over the next few years, which might be able to relieve depression and perhaps suicidality within hours after the first administration.⁵⁸ Open questions about these products comprise their long-term efficacy and safety, including risk of addiction and psychotropic effects; who would qualify for such therapies; and for how long. Meanwhile, psychosocial interventions could also be used as adjuncts to medication both for acute treatment and for maintenance therapy of bipolar depression.⁵⁹ The treatment of the depressive phase of bipolar disorder should always target clinical remission (because of the high relapse risk associated with residual symptoms) and functional recovery.

Treatment of rapid cycling and poor long-term response

Patients with bipolar disorder who have a poor response to available treatments in the longer term are a heterogeneous group. They do not respond well to treatment, mostly because they relapse frequently, do not recover in full from acute episodes, or both. This group includes people with rapid-cycling disorders, who, according to the DSM-5 definition, have four episodes or more per year. However, it also includes other forms of long-term refractoriness. Comorbidity is also the rule rather than the exception,⁶⁰ and suicidality is high.⁶¹ Some authors prefer to use staging frameworks to classify those patients, most of whom are at a late stage (stage IV). Hence, the management of such a subgroup of patients is particularly challenging.⁶² The evidence base is poor and there are discrepancies between treatment guidelines, but most agree that one of the first steps should be discontinuation of antidepressants. In rapid cyclers, several compounds have proven to be effective but only in the short term (a few weeks during an acute episode), and the long-term effectiveness has yet to be shown. Unsuccessful controlled trials include lithium, valproate, and lamotrigine monotherapy, probably because monotherapy is unlikely to work with any compound in this subpopulation.⁶³ Even combinations of two or three drugs tend to be unsuccessful.⁶⁴ Theoretically, the combination of several drugs with complementary mechanisms of action (eg, lithium and an anticonvulsant or a second-generation antipsychotic) would be one option, and maintenance electroconvulsive therapy is advised in acute responders to such therapy.⁶⁵ Psychoeducation might be helpful as well, but no controlled trial has been done in this subgroup. In general, patients at stage IV could be candidates for treatments such as clozapine, which unfortunately has

never been tested in randomised, placebo-controlled trials for this indication, as well as functional remediation therapies.⁷ The integral management of the illness along with the psychiatric and non-psychiatric medical comorbidities is crucial for a positive outcome. Rapid cycling and treatment resistance are not necessarily stable conditions, which is why they are classified as specifiers, rather than subtypes in DSM-5. Therefore, it is important to avoid therapeutic nihilism for any individual patient.

Functional outcome-oriented treatments

The first-generation evidence-based psychotherapies for bipolar disorder tried to address either acute symptoms, mostly depression, or prevention of relapse. Most of the success came from adjunctive maintenance packages, which have been further developed as combined online-delivery models and apps.⁶⁶ Second-generation therapies are focusing on functional outcomes, and most of those use metacognitive techniques, given the relevance of cognitive impairment for functionality.^{67,68} Although several trials are in progress investigating the effectiveness of cognitive remediation in the management of cognitive and functional impairment in bipolar disorder, one completed trial showed that functional remediation can effectively improve the psychosocial outcome of remitted patients with bipolar disorder and high disability.⁶⁹ This intervention improved functional outcome at the end of group therapy (21 sessions, once per week),⁷⁰ 6 months later with no booster sessions,⁷¹ and in patients with both bipolar type I and bipolar type II.⁷² Given that there is only one study on this intervention so far, the results need replication to support the findings. Functional remediation is delivered in a group format and has a neurocognitive and psychosocial background including modelling techniques, role playing, self-instructions, verbal instructions, and positive reinforcement, together with metacognition.

Improving the long-term course

Response prediction by personalised treatment

Precision medicine is a major goal in biomedical research. The focus for these initiatives is mainly non-psychiatric, but we believe that precision medicine will have an impact in mental illness. Bipolar disorder is highly heritable, and the growing number of large-scale genomic studies have started to identify risk genes in increasing numbers,²² and the explained variance of genetic risk loci is growing in parallel with increasing sample sizes in the Psychiatric Genomics Consortium. The latest genome-wide association study from the Psychiatric Genomics Consortium working group on bipolar disorder yielded 30 genome-wide significant loci, comprising genes for ion channels and neurotransmitter transporters (*CACNA1C*, *GRIN2A*, *SCN2A*, and *SLC4A1*), synaptic components (*RIMS1* and *ANKK3*), and immune and energy metabolism components.²² The emerging genetic knowledge has started to provide useful information about the underlying biology of the condition,²² and it

seems like bipolar disorder is a highly polygenic disease, with many genetic risk variants, each with a small effect. Furthermore, applying a genome-wide association study design, the Consortium on Lithium Genetics identified four linked single nucleotide polymorphisms on chromosome 21 (rs79663003, rs78015114, rs74795342, and rs75222709) associated with lithium response. The associated regions defined by these single nucleotide polymorphisms consist of two genes for long, non-coding RNAs; homozygous carriers of the response alleles had a statistically significant lower rate of relapse than heterozygous carriers in an independent prospective cohort.⁷³ Although these findings do not have any clinical utility yet, they suggest a large potential for new knowledge about the underlying disease mechanisms of bipolar disorder and response to lithium once more samples are genotyped and analysed.⁷⁴

In parallel with the novel genetic discoveries made possible because of new genotyping technology, technological advances in brain MRI and improved analytical methods have enabled new opportunities. The large international ENIGMA consortium assembled structural MRI scans from more than 6000 case-control samples of bipolar disorder. These studies have revealed distinct patterns of subcortical brain abnormalities in patients with bipolar disorders.⁷⁵ Furthermore, applying the same analytical pipeline, a clear pattern of cortical abnormalities was also identified,⁷⁶ with some association with the use of lithium. These findings are exciting because they suggest complex patterns of subtle brain abnormalities underlying bipolar disorders.

With the developments in genetics and brain imaging methods, it is not unrealistic to develop prediction and stratification tools for clinical use in bipolar disorder. Particularly, there is a clear need for developing brain imaging characteristics and molecular signatures in the blood for response to lithium treatment. Development of such biomarkers could represent potential tools that can be translated from research to clinical practice. There is a strong scientific rationale to apply front-line brain imaging, genomics and proteomics, and neurocognitive tools, alone or in combination, to establish the feasibility and cost-effectiveness of implementing these diagnostic methods in clinical practice. This is the goal of the newly initiated EU funded R-LiNK project. Other ongoing initiatives such as The Bipolar Illness Onset Study⁷⁷ are searching for personalised diagnostic markers with blood-based, neurocognitive, or behavioural biomarkers.

It is important to apply novel big data computational methods and statistical approaches to leverage the wealth of new information in bipolar disorders. Several approaches have been developed to improve prediction of clinical characteristics beyond prediction tools. The new Bayesian statistical approaches can increase the statistical power for detecting small genetic effects,⁷⁸ leading to the discovery of new susceptibility loci,⁷⁹ which are more likely to be replicable.⁸⁰ Furthermore, polygenic prediction

tools for neuropsychiatric disorders have a large potential for clinical utility.⁸¹ Such polygenic tools will also have a large potential for stratification of people to the right treatment, and other biomarkers or clinical characteristics can help with the prediction accuracy, as shown in 2017 for neuropsychiatric disease.⁸² Developing a similar approach for bipolar disorder has the potential to greatly affect clinical care.

Detection of early warning signs of mood episodes in long-term therapy

One of the key components of psychoeducation for patients with bipolar disorder or their relatives and caregivers, or both, is the early detection of warning signs of relapse. The ability to detect prodromal symptoms and behavioural changes preceding a full episode is key to prevent further morbidity, hospitalisations, and long-term cognitive impairment and disability. Moreover, the medication dose is often lower when used in prodromal symptoms than in the context of a full episode, and given that many side-effects are dose dependent, early detection also has benefits in terms of safety and tolerability. Early warning signs can be divided into general ones and specific ones. Among the general ones, insomnia or decreased need for sleep and increased irritability are common and can precede either depression or mania; the specific prodromes include changes in behaviour that are typical of a given individual but not necessarily common in other patients. For example, a patient might report an increased use of sunglasses, wearing hats, or smoking relapse preceding a manic episode. In many cases, a specific prodrome takes place every time that a given patient has a relapse, and therefore can guide early intervention.⁸³ This approach has been used in several psychoeducative packages. Perry and colleagues⁸⁴ reported the efficacy of tracking warning signs in the prevention of mania. Early detection is also a key aspect of the Barcelona intervention,^{25,85} and can be applied effectively in community settings.⁸⁶ In general, early intervention seems to work better for detecting mania than for depression, which is the same as saying that it has a high polarity index (an index of the antimanic versus antidepressive efficacy of various maintenance treatments for bipolar disorder).⁸⁷ Ideally, early detection of prodromal states should be combined with the promotion of illness awareness (insight is essential for early warning sign detection and adherence), education on the deleterious effects of illegal drug use, enhancement of treatment adherence, and encouragement of good habits related to sleep, diet, and exercise. All together, this strategy will enable patients and caregivers to foster their ability to prevent further episodes and improve the overall outcome of the disorder.

Interepisodic mood fluctuations

It is now recognised that, for many patients, the pattern of the illness does not fall neatly into discrete episodes of

For R-LiNK project details see
https://cordis.europa.eu/project/rcn/212676_en.html

mania and depression but is characterised by chronic, but variable, mood symptoms.¹⁴ This observation has immediate clinical importance and explains the substantial burden of illness experienced by many patients with bipolar disorder.⁸⁸ The initial insights were made through more intensive, careful retrospective assessment in a now classic series of studies, which identified that many patients have substantial episodic symptoms.^{89–92} The picture is beginning to become both clearer and more complex as the now widespread availability of connected and wearable devices (eg, smartphones) had led to digital phenotyping based on high-resolution measurement of remotely captured datastreams.⁹³ Indeed, it is recognised that chronic mood disorders provide an excellent exemplar of both the promise and challenge of digital health.^{94,95} Early studies have been small and, although promising, have yet to generate usable and validated clinical tools, while showing both the analytical and ethical challenges of these approaches.^{96–99} Nonetheless, this mood instability is increasingly recognised as a key therapeutic target¹⁰⁰ with the possibility of identifying patient-specific data signatures from the rich multidimensional datasets generated by each patient. These datasets could provide methods for early detection of severe destabilisation, empower the patients themselves, and ultimately provide a much more powerful and accurate phenotypic measure from which to establish the underlying mechanism.

Strategies to decrease excessive mortality

Life expectancy

There is a major knowledge gap regarding how to increase life expectancy in bipolar disorder. Standardised mortality among patients with bipolar disorder has consistently been found to be increased by two to three times compared with the general population.^{101,102} Life expectancy for the typical patient aged between 25 and 45 years decreased by 12·0 to 8·7 years for men and by 10·6 to 8·3 years for women.⁴⁰ Natural cause of death is the most prevalent reason for life-years lost already from adolescence, which increase substantially during early and mid-adulthood.¹⁰³ For 15-year-old patients with bipolar disorder, natural causes of death account for approximately 60% of all life-years lost, increasing to 80% at age 45 years.¹⁰³ These natural causes of death are comorbid general medical illnesses including cardiovascular disease,^{101,102,104} diabetes,^{102,105} and chronic obstructive pulmonary disease.^{102,106} Reasons for this increased mortality due to comorbid general medical illness in bipolar disorder could include unhealthy lifestyle factors including smoking, alcohol use, decreased physical activity,¹⁰⁷ disparities in quality of health care, adverse pharmacological effects from medication, and biological factors¹⁰⁸ such as accelerated ageing due to pathophysiological changes observed in bipolar disorder (eg, brain structural alterations, oxidative stress imbalance, and neurotrophic deficiencies).¹⁰⁹

Future studies in bipolar disorder should not only focus on improving the outcomes of the bipolar disorder but also on decreasing the risk of comorbid general medical illnesses.

Suicide prevention

As WHO stated in their report *The Global Imperative*,¹¹⁰ a comprehensive multisector suicide prevention strategy including universal, selective, and indicated interventions is the way forward for suicide prevention. This strategy includes the assessment and management of mental illnesses such as bipolar disorder, the restriction of access to means of suicide, and the development of policies to reduce harmful use of alcohol. Also, the role of the media and their use of responsible reporting practices for suicide plays an important part. Targeting susceptible groups (eg, those who have previously attempted suicide) by use of prevention strategies is another key approach.

Existing knowledge of individual risk factors allows the alignment of relevant interventions such as gatekeeper training and crisis helplines, but more importantly the assessment and management of mental diseases and suicidal behaviour. It has been estimated that approximately 25–50% of patients with mood disorders attempt suicide.^{111,112} Notably, a previous suicide attempt is the single most important risk factor for suicide. One year after a suicide attempt, the risk of suicide and premature death from other causes remains high.¹¹³ Furthermore, people with mood disorders have a 10-times higher risk of suicide than the non-psychiatric population.¹¹⁴ Bipolar disorder is estimated to have a 15–30-times higher risk of suicide than the general population.¹¹⁵ The risk of suicidal behaviour increases with comorbidity; individuals with more than one mental illness have statistically significantly higher risks than those with one or fewer. A major risk factor for suicide is alcohol dependence. Alcohol use and other substance use disorders are a factor in 25–50% of all suicides.¹¹⁶ Other risk factors for suicide were male sex, older age, job loss, financial difficulties, chronic pain, feelings of hopelessness, and a family history of a suicide attempt.¹¹²

Regarding pharmacological suicide prevention, evidence for the anti-suicidal effects of lithium has been consistently reported over the past 40 years.^{117,118} Data suggest that the high overall mortality in patients with mood disorders decreases by the use of lithium.¹¹⁷ Despite the recommendations in national and international guidelines for the acute and maintenance therapy of affective disorders, especially bipolar disorders, and the unambiguous evidence for its suicide prevention effect, the use of lithium is still under-represented. Lithium is a first-line option for the acute and maintenance treatment of mood disorders.¹¹⁹ Additionally, lithium should be considered as a treatment option particularly in patients at high-risk of suicide.¹²⁰

Search strategy and selection criteria

We identified references for this Review through PubMed searches for articles and previous reviews published from inception to Dec 1, 2017, using each of the key terms “early intervention”, “risk stages”, “high-risk studies”, “depression”, “suicide”, “mortality”, “life expectancy”, “polypharmacy”, “functional outcome”, “lithium response”, “genetics”, “response prediction”, “personalized treatment”, “mood fluctuations”, and “management”, in combination with the term “bipolar disorder”. Only articles in English were included. Articles identified by these searches that related to the main topics covered in the manuscript, and relevant references cited in those articles, were selectively reviewed.

Timely and effective access to health care is essential for reducing the risk of suicide.^{112,121} We still need to fight the stigma and taboo associated with seeking help for mental illness, which is leading to inadequate access to care and to a higher suicide risk in patients. Relevant intervention for people at risk includes repeated follow-ups (eg, after a patient is discharged) and community support. Training of health workers, with a focus on emergency care staff, is also needed.

Towards precision medicine for bipolar disorder

Despite the major gaps in knowledge on the basic mechanisms underlying bipolar disorder and the consequent broad range of unmet needs, we are optimistic about the prospect of advancement in the near future. The large-scale collaborative studies applying new methods will provide novel insights into disease mechanisms with the potential for the development of more targeted therapeutics.¹²² Innovation with digital technology has a particularly great potential to improve treatment and secondary prevention, and it is expected to see such digital tools in ordinary clinical use within a few years. A major obstacle to progress is the relatively low funding for research in the field compared with other diseases with similar morbidity, mortality, and global burden of disability. An increase in targeted funding opportunities in bipolar disorder is necessary, similar to that which is transforming research in dementia.

Contributors

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